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AUTOSENSITIZATION TO SKIN.

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"But how shall we expect charity towards others, when we are uncharitable to ourselves? Charity begins at home, is the voice of the world: yet is every man his greatest enemy, and as it were, his own executioner."

Sir Thomas Browne.

Religio Medici. Part II, Section IV.

It is well known that Whitfield (1921) in his second Lumleian Lecture expounded his concept of autosensitization. The concept of the potential pathogenicity of altered body components is foreshadowed by earlier writers, but to Whitfield belongs the credit of giving it form and a name. His definition of autosensitization as "a form of autointoxication derived from changes in the patient's own tissues", necessarily lacked precision. The term has found fame and fortune in the thought and writings of dermatologists, and is quite regularly applied as a diagnostic label to the sudden dissemination often without obvious provocation of a primarily circumscribed eczema. The concept has deeply influenced speculation on many of the unsolved problems of eczema. Ingram (1935), for example, suggested that there is probably "always a degree of autosensitization once the eruption is in being."

The tentative acceptance of the concept soon encouraged many investigators to attempt to support it by experimental proof. Parish (1960) has provided an excellent critical review of these early efforts, none of which was fully convincing, partly because contemporary immunological theory and experimental techniques were insufficiently advanced and partly because no rigid

definition of autosensitization was adopted. Sulzberger's definition formulated in 1940 is of interest as reflecting a phase in the development of modern immunological theory. "1. Alteration and liberation of organ specific antigenic irritants, created within the body from autochthonous organ tissues by various infective or non-infective agents. 2. Formation of organ-specific antibodies to these antigens. 3. The continuous or intermittent damaging effect of these antibodies upon the respective living organs *in situ*." The possibility that unaltered body components might provoke the formation of antibodies, with significant pathological effects, was not considered. Unfortunately, most dermatological investigators during the next two decades did not accept the salutary discipline imposed by Sulzberger's definition and their findings remain difficult to interpret. The various applications of the term autosensitization are nebulous. Autoeczematization, surely redundant both as a term and as a concept (Young, 1958), was loosely defined as "the process by which a widespread dermatitis may complicate several types of localized eczema."

The contemporary immunologist accepts a definition which is wide in its scope but precise in its limitations. A concise version recently employed by Parish (1960) will serve well for the purposes of the present discussion—"autosensitization is the sensitization of the body by circulating antibody, or a delayed cellular-type antibody, or both, to constituents of its own tissues." Immunologists are agreed that ideally before a disease can be confidently attributed to an autoimmune process, Witebsky's postulates should be fulfilled: free circulating antibody must be demonstrated by direct, or cell-based antibody by indirect means. The specific antigen against which the antibody is directed must be recognized. Antibodies must be produced against the same antigen in experimental animals. Pathological changes must be produced by these antibodies in the experimental animal.

It is the purpose of this paper to discuss the extent to which these postulates have been, or may be, fulfilled in relation to certain disorders of the skin, and to suggest which disorders may by analogy be considered as possibly dependent on autoimmune mechanisms.

Coombs (1960) has recently reminded us that the skin contains many large molecular substances which are potentially antigenic. In the epidermis, in addition to keratin, there are large globular proteins of plasma type and an individuality antigen is found on epidermal cells. Collagen is certainly antigenic as may also be the mucopolysaccharides of ground substance. The antigenicity of vascular endothelium is established. The antigens responsible for homograft rejection are nuclear and are common to all nucleated cells of the body. Since there are undoubtedly still other potentially antigenic components of skin I feel justified in interpreting my title liberally, by including those conditions in which the skin is prominently involved since the precise nature of the antibody has seldom been established.

Some knowledge of recent work on antibody formation is essential to an understanding of current theories of autosensitization. The facts on which the theories are based are derived from research in varied and seemingly remote fields—experimental genetics, carcinogenesis, homograft rejection and clinical medicine, in addition to immunology itself. Although the available facts are open to more than one interpretation, that masterly synthesis, which Sir Macfarlane Burnet has called the clonal selection theory of acquired immunity, provides us with a working hypothesis which illuminates many of the darker corners of medicine. Burnet himself emphasizes that the very ease with which so much can be explained by the application of this theory, should impose upon us some cautious restraint. Perhaps a fair analogy can be drawn with Selye's theory of stress which, although it has not solved as many of our problems as at first seemed probable, has none the less permanently altered our approach to them. The clonal selection theory will certainly be modified and probably superseded but not before it has shaken from us some of our cherished patterns of thought and replaced them by others less restrictive.

The direct template theory of antibody production is probably the most widely known. This postulates that antibody molecules have their specificity determined by being synthesized against the template of the antigen molecules themselves, the antigen thus enforcing certain cells to produce globular molecules carrying a complementary pattern. To us today the most important deficiency of this theory is its failure to account for the fact that antibodies to body components are not normally produced.

According to Burnet's theory, the capacity to produce a given antibody is not conferred by the antigen but is a genetically determined quality of certain clones of mesenchymal cells, the function of the antigen being to stimulate such cells to proliferation and antibody production. The chromosomes of all somatic cells are as liable to mutation as those of gene cells, and it has been estimated that some 100,000 mutational events take place in the body every day. Random mutation during early development will result in the initiation of many clones of mesenchymal cells corresponding to potential antigenic determinants in the body but these are eliminated by contact with the antigen during embryonic life. Thus all body components which either directly or as a result of the break-up of expendable cells can be present in blood or lymph cease to be antigenic to the individual himself. Immune tolerance, complete or partial, may also be induced to simple chemicals such as picryl chloride if the chemical is force-fed to pregnant guinea-pigs (Baer *et al.*, 1958) and the same mechanism explains the occurrence of blood chimaerism—the presence of erythrocytes of two distinct serological types—in non-identical cattle twins, and, as a great rarity, in human twins (Woodruff and Lennox, 1959).

The unitarian view of the mesenchymal cell is accepted, the phase assumed by the cell—stem cell, lymphocyte or plasma cell—being appropriate to local

conditions and functional requirements. The main function of the plasma cell is to produce gamma globulin. The lymphocytes carry genetic information and determine antibody specificity. They are the potential parents of plasma cells and the mediators of the functions of cell-borne antibody. They can be returned to mesenchymal cell aggregates and restored to the circulation several times in their life span. Thus if an antigenic determinant, as for example penicillin, makes contact with a lymphocyte of a mesenchymal clone which by random mutation has come to carry the appropriate complementary antibody, that clone is activated to proliferate and produce more lymphocytes. When the activated lymphoid cells make renewed contact with the antigen, a switch to the proliferation in the plasma-cell phase with production of soluble antibody may occur. It follows that innumerable individual clones randomly produced must fail to make contact with the appropriate antigen at the appropriate time and dwindle and disappear. Differences between individuals in the type or amount of antibody produced are related to inborn genetic differences.

Since mutation is random and continuous, inevitably throughout life clones of cells immunologically directed against body components will arise. These so-called "forbidden clones" are normally eliminated by homeostatic mechanisms.

The conditions in which autoantibodies might be produced and in which they might persist to give rise to pathological effects should now be evident.

(i) A body component may develop antigenic determinants through modification by chemical infective agents or pathological processes. The resulting antibody may be active only against the modified component or against both modified and normal component.

(ii) Pathological changes in a tissue may render accessible a previously inaccessible component which may then stimulate antibody production.

(iii) The homeostatic mechanism which normally ensures the rapid elimination of random forbidden mutations may fail. This failure may be temporary, as when the mesenchymal cells are modified by infection with a low-grade virus in infectious mononucleosis or atypical pneumonia. Mutation of mesenchymal cells to a form approaching or reaching malignancy may result in a more severe and sometimes permanent homeostatic failure. Other local or general disturbances may temporarily or permanently interfere with the elimination of forbidden clones.

Brief reference to Hashimoto's disease, lymphadenoid goitre, the auto-immune origin of which is generally accepted, may clarify some of these points. In this disease the first two of these three mechanisms are concerned. Damage to the thyroid, probably by an infective agent and possibly by a virus such as mumps, allows the previously inaccessible thyroglobin to become accessible. If random mutation has resulted in the formation of clones of lymphoid cells bearing the appropriate "sites" corresponding to the various thyroglobulin determinants,

the further production of these antibodies is stimulated. Antigen-antibody reactions give rise to inflammatory changes in the thyroid gland which becomes diffusely enlarged and infiltrated with lymphocytes and plasma cells. Cellular destruction in the thyroid renders accessible more previously inaccessible components and may set up a vicious circle. Of great interest is the wide variation in the titre of circulating antithyroglobulin antibody. In some cases none is detectable (Doniach *et al.*, 1960). The liberation of circulating antibody is clearly of secondary significance. The essential feature of this autoimmune reaction and probably of others I shall now consider, is the reaction of immunologically modified lymphoid cells with the normally inaccessible tissue components.

This brief summary does far less than justice to Burnet. The necessary omission of the mass of experimental evidence on which the theory is based may suggest quite unfairly that much of it is no more than inspired speculation. The possible mechanisms of homeostasis have not been discussed here and for a full account and a fascinating review of the supporting evidence, reference must be made to Burnet's own writings.

AUTOSENSITIZATION IN DERMATOLOGY.

(i) *Dissemination of a localized eczema.*

This syndrome is considered first, not because certain of its forms are more likely than other syndromes to be dependent on autoimmune mechanisms but because to most dermatologists the term autosensitization is closely associated with it. I have analysed the case records of 420 patients with eczema, excluding proved contact dermatitis and atopic dermatitis, but my findings agree so closely with many excellent published reports that they will be referred to only when they appear to throw light on details of possible immunological significance.

The classical "autosensitization" eruption follows chronic hypostatic eczema. Haxthausen's (1955) study of these cases is the most comprehensive. He found that the age of patients with a secondary eruption did not differ from that of his total series of 235 cases of hypostatic eczema, but that such eruptions occurred in 3 males to every 2 females. Dissemination frequently followed overtreatment or scratching or rubbing of the leg eczema, but in some cases—we have records of two such cases—dissemination occurred two or three days after the patient was admitted to hospital. It was invariably preceded by exacerbation of the leg eczema, which in these cases took place without obvious cause. Watson Smith (1945) made the interesting observation, which we have confirmed, that dissemination does not occur in widespread acute eczema of the leg or in the so-called stocking erythrodermas extending from toes or ankle

to knee. The primary eczema is of long duration but of limited extent. The secondary eruption develops explosively, pruritus may be moderate or severe, and there may be some malaise or anorexia. The secondary lesions are papules or papulovesicles, usually discrete, but sometimes forming plaques. The sites predominantly involved are the flexor aspects of the arms, the thighs and the trunk, and less frequently, the face, hands and neck. Recurrences are common. The histological changes are those of acute eczema. The conditions prevailing on the lower leg are such as could readily allow both the modification of potentially antigenic epidermal components and an increased accessibility of normally inaccessible components. In many cases the participation of either chemical or infective modifying agents is possible but in others seems clinically unlikely. This pattern of secondary dissemination may be accepted as compatible with an autoimmune response. However there is at present no reliable experimental evidence and most certainly there is no proof that the implication of autosensitization in such cases is not illusory.

The analysis of other patterns of dissemination of localized eczemas has proved singularly unrewarding and although several phenomena and sequences occur consistently enough to demand further investigation, they have been recorded by others (Brown, 1939 ; Vickers, 1952 ; Loewenthal, 1954 ; Hartung and Jansson, 1955) and appear irrelevant to our present theme. An exception is the not uncommon erythematous, papular or eczematous eruption which may follow a small circumscribed burn (Brown, 1939). In three of four such cases I have observed, there was no evidence of secondary infection or inappropriate treatment and the possibility of a reaction to altered skin components must be admitted.

The role of autosensitization in the dissemination of any other common patterns of eczema, including the discoid forms, is even more uncertain. Many useful investigations (Anderson, 1951 ; Rajka, *et al.*, 1953 ; Strempel, 1953 ; Röckl, 1955 and 1956) have been designed to assess the significance of bacterial sensitivity in such cases. Bacteria have certainly been conclusively incriminated in some cases but precisely what part they play in provoking dissemination remains undecided. Some investigators have failed to make clear the important distinction between bacterial sensitization and autosensitization. Bacterial products may so modify a skin component that it is no longer treated as "self" and can stimulate antibody production. If the antibody subsequently reacts with the unaltered skin component autosensitization has taken place. In bacterial sensitization, however, the skin merely provides the macromolecular carrier and the antibody is active against some antigenic determinant of the bacterial cell. Epstein (1952) in an interesting paper suggests plausibly that the pattern of reaction to the hapten, whether it be bacterial or chemical, may be modified by the nature of the macromolecular carrier, which he calls the "protigen", but of this, too, there is at present no proof.

(ii) *Exfoliative dermatitis.*

Exfoliative dermatitis occurs predominantly in patients over forty and is usually preceded by a localized dermatitis of long duration, often on the leg. (Gentele *et al.*, 1958). In about one-third of cases, the initial changes are eczematous. A malignant reticulosis is present in about one-sixth. Except in exfoliative psoriasis, the histological changes are identical whether the condition is primarily eczematous or secondary to a reticulosis (Wilson, 1954). Hyperglobulinaemia is usual. (Tickner and Basit, 1960).

All these characteristic features of exfoliative dermatitis suggest that an autoimmune mechanism may be involved. The extensive skin damage from overtreatment with external applications or the sensitivity reactions to arsenic or heavy metals, make accessible to the circulation modified antigenic determinants. When these meet cells of the appropriate clones, they stimulate the production of more antibody, which may react with unmodified antigen establishing a self-perpetuating vicious circle.

The presence of extensive disease of the mesenchymal cell system, impairing homeostasis, may allow autoantibody to persist. One can envisage a whole series of situations ranging at one extreme from the cases initiated by extensive exogenous skin damage, usually self-limiting as the normal mesenchymal cell system establishes homeostasis, to cases at the other extreme in which gross disturbance of homeostasis as in patients with malignant lymphomas, allows the establishment and more or less indefinite perpetuation of the autoantibody vicious circle.

The occurrence of exfoliative dermatitis in a boy with hypoglobulinaemia (Kay and Nelson, 1956) is not an argument against an autoimmune process. Children with congenital agammaglobulinaemia are particularly prone to develop rheumatoid arthritis which much evidence suggests to be an autoimmune disorder. Burnet suggests that lack of the protective effect of soluble antibody may be responsible, and draws an analogy with the blocking effect of classical type antibody against the pathogenic activity of hayfever antibody.

(iii) *Virus Infections.*

Reference has already been made to the capacity of certain low-grade virus infections temporarily to interfere with homeostatic control of autoantibody production. The cold agglutinins sometimes observed in atypical pneumonia and infectious mononucleosis were cited as examples. The skin eruption occurring in some 7% (Sadusk, 1941) of cases of infectious mononucleosis, maculopapular, urticarial or purpuric, and usually appearing between the fourth and tenth day, may have a similar origin. The Stevens-Johnson syndrome is often preceded or accompanied by atypical pneumonia and a search for autoantibodies in such cases might prove fruitful.

(iv) *Other diseases with Cutaneous Manifestations possibly dependent on Autoimmune Mechanisms.*

The list of diseases in which, primarily or secondarily, autoimmune processes are believed to play an important part is steadily lengthening. Some of those most carefully investigated from this point of view must be briefly referred to here although these may or may not be due to autosensitization to antigenic components of the skin itself.

a. The Collagen Diseases. Burnet believes that although the aetiology of the collagen diseases is complex and genetic, infective, immunological and stress factors may play a part, the assumption of a dysfunction of some of the cells producing antibody offers the most promising approach. The clinical picture may certainly be dominated by the consequences of the development of forbidden antibody patterns. The well established relationship of both dermatomyositis and scleroderma to malignant disease (Walton and Adams, 1958; Williams, 1959) may have an immunological basis and could profitably be further investigated along these lines.

b. The Reticuloses. Kaplan and Smithers (1959) have reviewed the evidence that the wasting, anaemia and lymphoid depletion observed in Hodgkin's disease, lymphatic leukaemia, lymphosarcoma and perhaps reticulum-cell sarcoma may be due to a cyto-immunological action of lymphoid cells against normal haematopoietic cells. The possibility that exfoliative dermatitis in these reticuloses may be the result of a failure in homeostasis has been mentioned. Other cutaneous manifestations, particularly those regarded as non-specific, may be of autoimmune origin and should be investigated as such.

c. Letterer-Siwe Syndrome. Burnett suggests that most features of this syndrome could be explained on the basis of random and variable output of forbidden clones and failure of homeostatic control.

(v) *Isoimmune Reactions.*

Homograft rejection is an isoimmune and not an autoimmune phenomenon and only its exceptional importance for the dermatologist justifies its inclusion in this discussion. Medawar (1959) has provided an outstanding review of our rapidly increasing knowledge of this and related phenomena. Boyd (1959) recently drew our attention to the concept that the mammalian foetus may be regarded as a homograft and suggested that unexplained abortion may be the result of homograft rejection. There is an increased foetal mortality rate in women with herpes gestationis (Russell and Thorne, 1957) but this could be regarded as the inevitable consequence of a severe systemic illness. However Keaty *et al.* (1951) recorded a foetal mortality of 30% in the twenty previous pregnancies of their ten patients with herpes gestationis, although the skin eruption was absent in thirteen of these pregnancies. The incidence of abortion in patients with the various prurigos of pregnancy (Kern, 1951) appears not

to be known. It is surely possible that herpes gestationis and perhaps certain prurigos will prove to be the consequences of incomplete immune tolerance of the foetal homograft. Those cases of herpes gestationis developing after delivery (Callaway *et al.*, 1946) could be the result of the access of foetal products after placental separation.

DISCUSSION.

Whether or not the theory of clonal selection be accepted in its entirety, it must surely be admitted that it points the way to constructive research into certain of the more obscure problems confronting the dermatologist. Witebsky's postulates were quoted with no cynical intent but to focus attention on the gap yawning between the theoretical probability that autosensitization determines many of the common clinical phenomena of dermatology and the goal, as yet unattained in respect of any one of them, of acceptable scientific proof.

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LABORATORY INVESTIGATIONS OF AUTOSENSITIZATION TO SKIN.

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THE object of this paper is to present a general description of the immunological techniques available for the study of the problem of autosensitization to skin, with some of the advantages and disadvantages associated with their use. In order to illustrate the application of these techniques to a study of a disease in man in which autosensitization is induced, examples have been taken from recent studies on Hashimoto's thyroiditis, otherwise called autoimmune thyroiditis or lymphadenoid goitre.

The use of the term "autosensitization to skin" is still largely a clinical concept as when it was first introduced by Whitfield (1921), and there is insufficient immunological evidence that sensitization of an individual to his own skin tissues does take place. This problem is now being studied by the techniques to be described and a summary of the results of experiments carried out in collaboration with Dr. Rook and Dr. Champion is presented, in which two patients with generalized dermatitis appear to have circulating antibodies to their own skin.

DEFINITIONS.

For the moment, the definition of hypersensitivity proposed by Coca (1920) is still acceptable, viz., "hypersensitivity is a condition of specific or particular reactivity, with characteristic symptoms, to the administration of or contact with any substance in a quantity which to the rest of the individuals of the same species is innocuous". Such a definition incidently, includes some forms of hypersensitivity in which the abnormal sensitivity is not known to be of immunological origin.

An immunological state of hypersensitivity is the result of stimulation by antigenic material, such that further exposure of the body, or an organ or particular tissue to the same antigen, results in changes of a type not encountered when that antigen is administered to an individual never previously exposed to it.

The sensitized animal body may respond to the presence of the specific antigenic material in a number of ways, which are conveniently considered under the headings of immediate type and delayed type sensitivity, according to the time interval and the nature of the response following introduction of antigen

to the sensitized body. In general terms, these two forms of sensitivity have the following basic characteristics.

Immediate type.—(i) A sensitivity associated with the presence of circulating antibody of the precipitin type which may be demonstrated by at least one *in vitro* method, and which can be transferred to a normal subject in the serum.

(ii) A sensitivity associated with circulating antibody of a non-precipitating relatively heat-labile type, commonly associated with natural sensitivity in hay fever and asthmatic conditions, and which cannot be demonstrated consistently by any *in vitro* method, though it has strong tissue sensitizing properties which can be passively transferred.

Delayed type.—The classic example is the tuberculin reaction, in which the immunological response is dependant upon the leucocytes and passive transfer of the sensitivity can only be achieved by the leucocytes or fractions thereof.

The heat-labile non-precipitating antibody is conveniently termed reagin, but the conditions with which it is commonly associated were once considered to be distinct from hypersensitivity of the anaphylactic type and described as atopies and the specific antigens as atopens (Coca and Cooke, 1923). This misleading distinction is now being abandoned.

In dermatology, however, the term "atopic dermatitis" is used in another context to describe a condition in individuals with certain clinical manifestations which have no demonstrable immunological basis. The formation of antibodies, reaginic or precipitating, is considered not to be the cause of the dermatitis in the majority of these patients (Cooke, 1944; Pettit, 1954; Meara, 1955).

In the process of autosensitization, the body reacts to some part of its tissues in the same way as a sensitized body may react with a specific extraneous or foreign antigen as described above. Autosensitization is the sensitization of the body, by circulating antibody, or a delayed cellular-type reaction, or both, to constituents of its own tissues. In the process of autoimmunization, the sensitizing antigens must also be constituents of the individuals' tissues. In this context it should be remembered that the components of plasma and other body fluids are cellular products.

It is essential to demonstrate that the specific antigens are components of the individual's own body before accepting the presence of circulating antibody capable of reacting with some organ as evidence of autosensitization. This is of particular importance in investigations of the skin which is continually exposed to foreign material and micro-organisms of the environment, and is constantly subject to minor degenerative processes. Some of these problems encountered in the human patient and experimental animals have been reviewed previously (Parish, 1960). Even when the effects of external factors can be eliminated, there remains an extensive range of potential antigenic components in the skin, as has been described by Coombs (1960).

Certain criteria therefore become necessary before an autoantibody can be accepted as of any pathogenic significance in a particular disease, and Witebsky, Rose, Terplan, Paine and Egan (1957) have suggested that, where possible, the following conditions should be fulfilled.

(i) The direct demonstration of free, circulating antibodies that are active at body temperature or of cell-bound antibodies by indirect means.

(ii) The recognition of the specific antigen against which this antibody is directed.

(iii) The production of antibodies against the same antigen in experimental animals.

(iv) The appearance of pathological changes in the corresponding tissues of an actively sensitized experimental animal that are basically similar to those in the human disease.

The immunological techniques available for the investigation of the phenomenon of autosensitization are reviewed in the following order : agglutination, precipitation, complement fixation, fluorescent markers, skin testing and tissue culture.

Agglutination.—Agglutination is the most sensitive means of detecting antibodies of the precipitin type. Particles or dispersible cells having antigens in common may be agglutinated by specific antisera when the antigens lie on the surface of, or are incorporated in the cell wall. However it is possible to coat dispersible particles with soluble antigenic material that is not present in the cell wall, and carry out agglutination tests using them as the indicator system. One technique of this type is the use of erythrocytes treated with tannic acid and coated with the test protein or protein complex as described by Boyden (1951). It is an extremely sensitive technique and has been used to detect autoantibodies in human sera for a number of different organs, notably Hashimoto's thyroiditis for which it appeared to be the most sensitive means of detecting antibodies (Witebsky *et al.*, 1957).

As in all serological procedures, it is essential to control the specificity of the reaction, particularly as extracts of some tissues used to coat the tanned cells may cause a certain amount of clumping. This has been found to occur when some extracts of human skin have been used as the antigen, though this tendency may be mitigated or abolished by prior ether extraction of the antigen.

Agglutinins have been detected to human skin in material from two subjects, but the nature of the specific antigen or antigen complex has not been determined. The tanned cell test has the advantage that the cells may be coated with any protein elements present in the extract, though Borduas and Grabar (1953) have found that there may be some selectivity in the uptake of the proteins present.

It is also possible to examine sera for antibodies to polysaccharide antigens, by using untreated erythrocytes as described by Middlebrook and Dubos (1948).

Another technique that is beginning to have a wide application to the study of tissue antigens is the mixed cell agglutination technique which was used by Coombs, Bedford and Rouillard (1956), to demonstrate the presence of the A and B blood group antigens on human epidermal cells. This technique consists essentially of the demonstration of the common antigen or antigens present on the surface of the test cells, and the cells of the indicator system, for example erythrocytes known to contain the specific antigen, using specific antisera to bring about agglutination. Modifications of this delicate technique are going to play an important role in the study of surface antigens on cells and their relationship to species and even organ specificity. For this reason it will be of value to consider what has already been accomplished by the technique.

The method has been used to demonstrate the presence of the A and B and other blood group antigens on platelets (Coombs and Bedford, 1955 ; Ashhurst, Bedford and Coombs, 1956), on spermatozoa (Gullbring, 1957), on leucocytes (Gurner and Coombs, 1958), foetal kidney cells in tissue culture (Högman, 1959) and HeLa cells (Kelus, Gurner and Coombs, 1959). It has been employed to determine the presence of the A antigen on buccal cells of some rabbits (Hawes and Coombs, 1959) and more recently it has been used to determine the species of origin of cells in tissue culture (Coombs, Daniels, Gurner and Kelus). No evidence was gained by the use of this technique that other blood group antigens investigated existed on human epidermal cells (Ashhurst, Bedford, Coombs and Rouillard, 1956) though the presence of the A and B antigens was confirmed by another serological technique employing the absorption and elution of isoagglutinins (Nelken, Gurevitch and Newman, 1957).

Yet another variation of the techniques of agglutination is the mixed cell antiglobulin test used by Coombs, Marks and Bedford (1956) to detect the presence of antibodies on platelets, and has been applied to the detection of iso-antibodies on a number of human cell types (Chalmers, Coombs, Gurner and Dausset, 1959 ; Garrett, Giles, Coombs and Gurner, 1960).

Should a cell be sensitized by an antibody to some surface antigen whose identity need not be known, it may be possible to detect its presence by adding indicator cells, e.g. erythrocytes sensitized by non-agglutinating antibody of the same species, and the specific antiglobulin sera, which should result in mixed cell agglutination.

Unfortunately it has not been possible to utilize this technique for the detection of sensitizing antibody on epidermal cells in the present study, as it has been found that human epidermal cells of the stratum malpighii may retain traces of globulin on their surface when isolated, and have a strong

affinity for any normal globulin to which they are exposed. Similar experiments on normal guinea-pig epidermal cells, using guinea-pig erythrocytes to which globulin had been chemically linked as the indicator system, indicate that the same non-specific absorption of globulin *in vitro* by epidermal cells may also occur in this species.

Precipitation.—Precipitation tests have been used since the early days of serology to detect the presence of antigen in solution or antibody and modifications of the techniques of double diffusion in gel media introduced by Oudin and Ouchterlony have been widely used in the study of autoimmunity, particularly by many workers investigating Hashimoto's thyroiditis. However, the application of these techniques to many problems revealed certain limitations. Ouchterlony (1953) described a valuable method of recognizing patterns of identity, partial identity and non-identity in the single precipitation lines resulting from the interaction of antigen and antibody in gel plates. Subsequent workers discovered that any one antigen-antibody complex may under certain conditions produce multiple lines even when highly purified antigens have been employed, and Korngold and van Leeuwen (1959) have presented one explanation with experimental evidence that this results from precipitates being found in antigen or antibody excess, and further diffusion of free antibody, antigen or soluble antigen-antibody complexes to form new precipitation lines. Jennings (1956) has also indicated a nicety in the interpretation of a precipitin line when antibody combining with a protein, and antibody combining with a hapten attached to the protein would result in a misleading reaction of identity.

A more serious potential source of error in the interpretation of experimental data has been described recently by Berenbaum, Kitch and Cope (1960) who found that sera taken from normal rats or other experimental animals were capable of producing precipitation lines in gel plates against extracts of the animals' own tissues. The nature of this reaction is still under investigation, but it does emphasize the need for caution, and the strict control measures necessary when investigating immune responses in disease.

Complement fixation.—Complement fixation tests have long been a method of choice for the detection of antibodies or tissue antigens, and when tissue constituents are used as antigen this test has the advantages that the extract containing antigen need not be pure, and that the antigen may be in particulate or soluble form. It has been possible to demonstrate a number of organ specific antigens and even to differentiate two parts of the same organ, as for example the anterior and posterior lobes of the pituitary (Witebsky and Behrens, 1932).

The fixation of complement by a mixture of serum and tissue extracts is not conclusive evidence that specific antibodies are present in the serum. Haemolytic complement fixation tests have revealed the presence of antibodies, or antibody-like factors in the sera of individuals reacting with the

host's own tissue. Kidd and Friedwald (1942) described a "natural tissue antibody" in the serum of a large number of normal rabbits which fixed complement in the presence of a constituent of normal tissue cells from a number of the organs of the same animal, or even of a different species. A similar finding has been observed in man, in which a haemolytic complement fixation test revealed complement fixing factors in sera for human tissue homogenates. There was no strict organ nor species specificity, neither was the presence of the "autoantibody" restricted to diseases presumed to be of autoimmune nature, for sera from some normal individuals occasionally gave a positive test (Gajdusek, 1958; Mackay and Gajdusek, 1958). These findings have been confirmed (Hackett, Beech and Forbes, 1960) but it is suggested that the fixation of complement may have resulted from some lipid interaction, changes produced by heat inactivation of the sera, enzymic artefacts or a non-immunological alteration in specific globulins, in the absence of any specific antibodies.

However, specific complement fixing antibodies have been described in autoimmune disease in man, in cases of Hashimoto's thyroiditis (Witebsky *et al.*, 1957; Trotter, Belyavin and Waddans, 1957), and appear to be directed against the microsomal fraction of the cells of the thyroid (Roitt and Doniach, 1958) though two complement fixing antibodies of different specificity may be present (Anderson, Goudie and Grey, 1959).

In experiments investigating the possibility that individuals may become sensitized to their own skin, an eluate was obtained from the skin of one patient which would fix complement in the presence of the skin homogenate (Parish, 1960). It was later demonstrated that complement was fixed in the presence of antigen extracts from the skin of five individuals, and the factor could be neutralized by absorption with skin cells. No fixation of guinea-pig complement occurred in the presence of extracts of liver, kidney or spleen and these extracts could not inhibit the fixation of complement by extracts of skin.

Fluorescent markers.—The fluorescent marker technique of Coons and Kaplan (1950) and Coons (1956) enables either antibody or antigen to be traced within particular cells of a tissue, and can give an indication of their site within the cell. Using fluorescein labelled antibody, Tanaka and Leduc (1956) demonstrated the presence of the Forssman antigen in the tissues of several species, and Glynn and Holborow (1957, 1959) and Szulman (1960) traced the distribution of blood group substances in human tissues. Szulman found that labelled human isoantibodies anti A and anti B were taken up by the walls of the cells of the upper half of the Malpighian layer of the skin and the granular layer, while the basal layer remained relatively free. A similar technique has been used to compare the antigens of human skin and some related tumours by Hiramoto and Pressman (1957) who used labelled heteroantibodies.

This technique has already proved to be of great value in detecting the sites of localization of the autoantibodies from the sera of patients with autoimmune thyroiditis (White, 1957; Beutner, Witebsky, Rose and Gerbasi, 1958). White used the thyroid gland and serum from the same patient thus eliminating possible cross reactions by isoantibodies and he was also able to demonstrate the presence of antibody in cells of the adjacent lymph nodes using labelled antigen.

Skin testing.—The skin of a specifically sensitized individual may respond in one or more of three essential patterns to an intradermal injection of the antigen.

(i) There may be an immediate type of reaction attaining a maximum in about 20 minutes and characterized by a wheal and erythematous flare, such as is commonly observed in patients naturally sensitive to certain pollens.

(ii) There may be a semi-immediate type of reaction which requires 18 to 24 hours to attain its maximum response and then begins to regress. This reaction is associated with the presence of circulating precipitins and appears to be an Arthus type of response. It has been observed in patients with circulating precipitins to fungi, and also in subjects with precipitins in their sera to thyroid antigens (Buchanan, Anderson, Goudie and Grey, 1958).

(iii) The third pattern of response is the delayed type of sensitivity as observed in the indurated lesions of the classical tuberculin response, which may reach its maximum size in 48 to 72 hours.

There are many factors which may influence the result of such tests and which are capable of inducing a response falsely attributed to be the effect of the interaction of antigen and antibody; some of which have already been reviewed with reference to autosensitization to skin (Parish 1960).

One of the accepted characteristics of an antibody is its capacity to be neutralized by the specific antigen. But when injections of mixtures of antigen and antibody are made into the skin, immediate type reactions may be elicited which are not confined to the activity of one particular form of antibody. For instance, a mixture of human reagin and its specific antigen injected into human skin will produce an immediate type reaction (Gay and Chant, 1927; Foran and Lichtenstein, 1931; Harley, 1933; Cooke, Barnard, Hebal and Stull, 1935; Loveless, 1940). The cause of this reaction is not known though Kuhns and Pappenheimer (1952) demonstrated that human reagin diphtheria antitoxin may be neutralized *in vitro* by toxoid, but the mixture was an irritant to the skin of normal individuals. The precipitate of precipitating type antibody and antigen is also capable of inducing a skin reaction and Opie (1924*a, b*) induced an Arthus type reaction in rabbits 24 hours after the intracutaneous injection of the precipitate. Furthermore, soluble antigen-antibody complexes will cause an immediate type reaction in the skin of guinea-pigs previously injected with dye intravenously as an indicator. This response appears within a few minutes and reaches its maximum in 30 minutes (Trapani, Garvey and

Campbell, 1958 ; Ishizaka and Campbell, 1958). Evidence has been obtained that the antibody in these complexes may alter to develop a toxic configuration (Ishizaka and Campbell, 1959 ; Ishizaka, Ishizaka and Campbell, 1959), but Rosenberg, Chandler and Fishel (1958, 1959) present other experimental evidence that the response is cutaneous anaphylaxis, either due to the failure of all the antibody sites to be saturated or as a result of dissociation of the complex.

Immediate skin reactions may also follow the injection of heat inactivated normal human sera. Christian (1960) found that aggregates of human gamma globulin formed by heating the globulin at 56° C. for 30 minutes would produce a wheal and flare response on intracutaneous injection of three human subjects within 10 minutes of injection and an increased vascular permeability 30 minutes after intracutaneous injection of guinea-pigs which had received an intravenous injection of dye, but that fractions of human gamma globulin which did not contain these aggregates produced no significant reaction.

In studies on autosensitization to skin in man, samples of blood taken from one patient during the course of generalized eczema, and which contained agglutinating antibodies to human skin, produced a definite immediate type reaction on intradermal injection into the patient, even if the serum was dialysed, whereas a sample taken after the eczema had resolved and tested at the same time, contained no agglutinating antibodies and had no effect on intradermal injection.

These sera have been injected into the skin of a normal volunteer. The first sample containing antibody produced a distinct wheal and flare, even if absorbed with fresh human liver or spleen cells, but the second sample, and the first sample absorbed with fresh intact human epidermal cells produced no significant response.

When this first sample containing antibody was mixed with a soluble extract of human epidermal cells, and the mixture injected into the skin of the normal volunteer, a very strong immediate type reaction was obtained. An understanding of the potential toxicity of antigen-antibody complexes is therefore important, for as will be described later, this sample of serum contained heat stable agglutinating antibodies and a heat labile cytotoxic factor to human skin. The active serum produced an immediate type skin response on intracutaneous injection of a normal individual, and this effect could be abolished by absorbing the serum with intact human epidermal cells, but the addition of a soluble extract of human epidermal cells to the serum resulted in an even greater skin response when the mixture was injected, though the soluble extract by itself was innocuous.

Under the heading of skin testing may be included a short reference to an experiment of Voisin and Maurer (1955) in which rabbits injected with skin from donor rabbits and which subsequently rejected homografts from the same animals later tended to reject autografts of their own skin.

It is possible that the process of autotransplanting skin may render accessible antigens that are normally protected from the lymph and blood, and that the vascular proliferation in the bed of the graft would be associated with the infiltration of lymphocytes and cells of the macrophage-fibroblast series.

Tissue culture.—Since the demonstration by Rich and Lewis (1932) that tuberculin could cause cytopathic changes and inhibit proliferation of explants of tissues taken from tuberculous guinea-pigs, there have been a large number of experiments to demonstrate cytopathic changes in tissues in relation to both the delayed and immediate type of sensitivity. Many of the reports of such experiments are conflicting, and to some extent, this must be due to the difficulty encountered in attempting to standardize the cells in the tissue culture systems.

Living tissue cells will vary morphologically and biochemically with the conditions of their environment, and results obtained under any one set of conditions are not strictly comparable to those obtained from cells in another environment. Tissue cells in the living body are not identical with those growing in fresh explants, and established cultures differ greatly from newly isolated cells. Even cells of short term cultures, obtained from man or animals, quickly develop morphological changes especially in the nucleus (Berman, Stulberg and Ruddle, 1957; Kleinfeld and Melnick, 1958; Larin, 1958; Larin, Barr and Orbell, 1959). Thus it becomes difficult to determine the significance of some of the changes noted under experimental conditions and any change in the pH or the media imposes a new set of conditions upon the system. There have been many experiments to determine the effects of immune sera on cells in tissue culture but little has been done to observe the effects of autoantibody on the host's cells. However cytotoxic effects have been demonstrated in sera from cases of Hashimoto's disease on freshly isolated human thyroid cells in tissue culture (Pulvertaft, Doniach, Roitt and Hudson, 1959). This antibody was heat labile and therefore different from the agglutinating and complement fixing antibodies. Cytotoxic effects of pig serum containing autoantibodies to skin have also been reported (Parish, 1960). These sera incorporated in the media of tissue cultures of explants of autologous skin and regional lymph nodes induced cytopathic changes in the living cells, and there was little proliferation of these explants.

Cytopathic changes have been observed recently in cells from a freshly excised skin explant, consisting for the most part of epidermal cells removed from a clinically normal area of skin of a patient with generalized eczema. These cytopathic changes were induced by her own serum. When the serum was incorporated as 10%, 33% or 50% of the medium added to the explant there was no proliferation from the explant, but explants in media containing similar quantities of normal serum developed nests of proliferating cells. If the medium containing the patient's serum was removed at this time, and replaced

by medium containing normal control serum, the explant still failed to develop any cellular outgrowth.

These changes commenced in the first to second minutes of observation under phase contrast and consisted of a shrinking of the mitochondria which became surrounded by pale vacuoles, and during the next 15 to 30 minutes the cytoplasm became opaque and the cell wall began to retract. The nucleus also became opaque and it was no longer possible to determine its interior structure, but the changes in the nucleus appeared less severe and always appeared after the cytoplasmic changes. In a few cells in the terminal stages the cytoplasm appeared to exude out of the cell as the cell wall contracted. The end result was a shrunken ghost cell, either too opaque to observe any interior detail, or containing a shadowy pyknotic nucleus in an amorphous cytoplasm. The changes were usually complete in any cell within an hour, but not all the epidermal cells of the cultures appeared affected though initially they appeared to be morphologically identical. Lymphocytes, polymorphonuclear leucocytes and large amoeboid macrophages added to the system remained unaffected. The longer the cells of primary culture were kept before challenge with the patient's serum, the fewer appeared to be susceptible to the serum, though it became very difficult to determine the origin of many of the proliferating cells, and in the first subculture there were very few susceptible cells.

The serum factor appeared to be a gamma globulin; it was heat labile, being destroyed by heating the serum at 56° C. for 30 minutes and was not reactivated by the addition of fresh human complement. It had no toxic effect on HeLa cells, and could not be absorbed out by a suspension of HeLa cells or fresh human leucocytes, but it was absorbed out by homologous, living partially separated skin cells.

It is not easy to decide whether a factor in serum producing cytopathic or cytotoxic changes in cells in tissue culture is a specific antibody, and criteria are being evolved from these experiments and will be published later. This sample of serum contained agglutinating antibodies to the patient's skin, but they were heat stable, and the factor causing cytopathic changes was heat labile and therefore different from the agglutinating antibody.

SUMMARY OF EXPERIMENTS INVESTIGATING AUTOSENSITIZATION TO SKIN.

Material was taken from cases of generalized eczema in which an initially circumscribed eczema had undergone widespread secondary dissemination; the pattern which by a modification of Whitfield's (1921) concept, dermatologists have tended to attribute to autosensitization. This material was subjected to many of the experimental techniques described, and in two subjects evidence has been obtained, in no way conclusive, that autosensitization to the patient's skin was present at the time of the disease.

The first subject, from another series of investigations, was a case of exfoliative dermatitis, in which no antibodies in the serum to autologous or homologous skin could be determined by the tanned cell test, but eluates of preparations of the patient's

skin contained a factor which had a low agglutinating titre to autologous and homologous skin extracts.

When this factor was concentrated it was found to be capable of fixing guinea-pig complement in the presence of autologous skin extracts, and extracts of skin from five other individuals both normal and eczematous. This factor could be absorbed out by suspensions of fresh epidermal cells. No fixation of complement occurred with extracts of liver, kidney or spleen, and these could not inhibit the fixation of complement to skin extracts.

The second subject was a case of generalized eczema, and the investigations are not yet complete. A sample of blood drawn during the course of the disease was found to have agglutinating antibodies to normal homologous skin extracts, and which could be neutralized by skin extracts; a sample of blood taken after the patient had recovered contained no agglutinating antibodies. On two occasions intradermal injection of the first sample into the patient produced a positive response. The samples of serum were used both dialysed and undialysed against physiological saline and were demonstrated to be free of any histamine-type activity by tests on guinea-pigs' tissue.

Injection of the first sample of serum into the skin of a normal volunteer produced an immediate type reaction, which was not removed by absorption of the serum with intact human liver nor spleen cells, but was absorbed out by normal intact human epidermal cells. Injection of the second sample of serum produced no skin response.

Cytopathic changes were observed in explants of the patient's own skin in the presence of the first sample of serum, and the serum factor was heat labile and therefore different from the agglutinating antibody. It was not absorbed out by suspensions of washed HeLa cells or fresh human leucocytes, but was removed by absorption with fresh separated human epithelial cells.

The significance of these results and their relationship to any disease process is still to be determined.

SUMMARY.

An account is given of the immunological techniques available for the investigation of autosensitization to skin, together with some of the advantages and disadvantages associated with their use. Material obtained from two patients provided evidence that autosensitization to skin may have occurred.

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ESSENTIAL CRYOGLOBULINAEMIA.

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WINTROBE AND BUELL (1933) were the first to report the observation of a protein in plasma which precipitated at temperatures less than 37° C. The protein was first observed in a haematocrit above the layer of packed red cells. It appeared as a yellowish-grey gelatinous material. When the haematocrit tube was placed in the refrigerator, an additional cloudy white material appeared in the plasma above the gelatinous layer. This substance disappeared at room temperature in 10 to 15 minutes. Their case was one of multiple myeloma which presented with extensive purpura, Raynaud's phenomenon and retinal vein thrombosis.

This observation of a cold precipitable substance in the plasma was later repeated by several investigators, Von Bonsdorff (1938), Bing (1940), Stein and Wertheimer (1942), Holmberg and Gronwall (1942), Wertheimer and Stein (1944), Flemberg and Lehmann (1944).

Lerner and Watson (1947) proposed the word "cryoglobulin" (κρύος, icy-cold) for this cold precipitable protein of the serum. Since 1947, cryoglobulins have been shown to occur in a wide variety of diseases including multiple myeloma, solitary plasmacytoma, kala-azar, cirrhosis of the liver, lymphosarcoma, lymphatic leukaemia, lupus erythematosus and polyarteritis nodosa. Multiple myeloma is the commonest condition associated with significant amounts of this protein and in which symptoms seem to be directly attributable to its presence. There are, however, a small group of cases with symptoms attributable to the presence of a cryoglobulin in which no underlying disease process has been demonstrable. Such cases of "essential cryoglobulinaemia" have been described by Barr *et al.* (1950), Steinhardt and Fisher (1953), Hutchinson and Howel (1953), and Pelzig (1954). Volpe *et al.* (1956) described a case with a twenty-five year history and gave an excellent review of the literature. Barnet *et al.* (1956) described a case with purpura and ulceration of the lower limbs induced by cold, while Cable *et al.* (1958) described a similar patient who died ultimately from coronary thrombosis.

The rarity of these cases of "essential cryoglobulinaemia" coupled with their interesting symptomatology has prompted us to describe a further example.

CASE REPORT.

A woman aged 66 years was first admitted to the Royal Masonic Hospital in February 1957 and was re-admitted in June and September, 1959. Ten days after her discharge in September, 1959, she was admitted to hospital near her home as an emergency with acute myocardial infarction and died. Autopsy there confirmed the cause of death, but no evidence of any other disease was found.

In 1957, she gave a six-year history of recurrent ulceration of the legs especially around the ankles. She related the onset of the ulceration to a number of severe bites which she thought were due to mosquitoes. For three months prior to admission, purpuric lesions had appeared on the hands, both elbows and the lobes of both ears, but these had subsided without ulceration. In the legs, the sequence was of petechiae gradually coalescing to form painful purple nodules which subsequently underwent

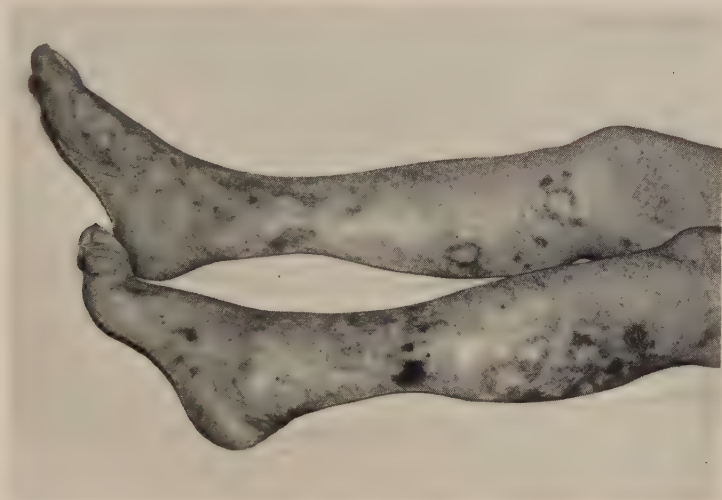


FIG. 1.

ulceration. The ulceration was always more severe in the winter, but tended to heal during the spring and summer. For several years she had noted undue sensitivity to cold and during the previous summer the ulcers had failed to heal. She had been treated with systemic and topical antibiotics and steroids without any improvement.

Examination revealed multiple discrete superficial ulcers of the legs intermingled with areas of pigmentation and the anaesthetic atrophic scars of previous lesions (Fig. 1.) Raised purple nodules were present on the arms and the ulnar borders of both forearms. There was no evidence of varicose veins, the skin temperature of the legs was normal and all the accessible peripheral pulses were present and of good volume. The blood pressure was 190/96 mm. Hg. with some cardiac enlargement, but normal heart sounds. The optic fundi showed vascular sclerosis, but no other abnormality.

Progress.—Soon after admission to hospital, the patient developed acute pain and blanching of the terminal phalanx of the left middle finger. Gangrene soon developed, and amputation had to be carried out through the middle interphalangeal joint. At the same time, biopsy specimens were taken from the left quadriceps muscle and from an area of recent cutaneous ulceration in the leg. Treatment with systemic steroids and vasodilators was ineffective, but there was gradual healing of the lesions with the early summer.

Her two subsequent admissions were after episodes of cerebral thrombosis and congestive cardiac failure respectively: she made a good clinical recovery with rest in bed, diuretics and digitalis. On each occasion, fresh skin lesions were present on the legs, but these cleared during her stay in hospital. Over the two years that we observed her, there was a gradual rise in the diastolic blood pressure from 96 to 110 mm. Hg. The application of an ice-pack to the skin of the back for up to two minutes produced only transitory colour changes.

Investigations.—(Summarizing those of three admissions).

Hb. 86% dropping gradually to 60%. P.C.V. 29%. M.C.H.C. 30%. E.S.R. (Westergren) 30–85 mm. in first hour. Platelets 195,000–242,000 per cu. mm. Marrow puncture showed marked erythroid activity, but no evidence of myelomatosis. Cold antibodies were not present. L.E. cells were searched for on numerous occasions, but could not be demonstrated. Blood Wasserman and Kahn negative. Osmotic fragility of red cells normal.

Whole serum taken and separated at 37° C. gave the following values. Total serum protein values were always normal, being 6.3 g./100 ml. (albumin 3.95 g./100 ml., globulin 2.35 g./100 ml.) in 1957 and 6.7 g./100 ml. in 1959. The globulin content increased however, so that in 1959 it was greater than the albumin (albumin 2.84 g./100 ml., globulin 3.90 g./100 ml.). This increase in globulin was mainly in the gamma globulin fraction as judged from the electrophoretic strips.

Although some cryoglobulin could be detected in blood taken and separated at room temperature, maximal amounts were obtained when the whole operation was performed at 37° C. If the blood was taken at 37° C. but then centrifuged at room temperature, even for very short periods, considerable amounts of cryoglobulin were lost from the supernatant.

After separation, the whole plasma or serum was divided into two portions, one being kept intact at 37° C. and the other cooled and further separated into a cryoglobulin free supernatant and a cryoglobulin deposit. Evidence of cryoglobulin precipitates as shown by increasing turbidity of the plasma or serum was apparent even at 33° C. but for maximal separation it was necessary to cool it to 4° C. for 12 hours or so. After this time, no further precipitation could be obtained even on further cooling. In the refrigerator, precipitation began virtually immediately.

We were never able to separate the cryoglobulin other than as an amorphous deposit. It would redissolve on warming and re-precipitate on cooling. We estimated its concentration by the difference in the total protein values of the whole serum and the cryoglobulin free supernatant using the micro-Kjeldhal method. The highest values obtained was 0.5 g./100 ml. whole serum; the lowest was 0.38 g./100 ml. Dr. A. S. McFarlane at the National Institute for Medical Research noted that the purified cryoglobulin was soluble in saline at 37° C. to more than 11 mg./ml. and that on cooling such a solution to zero, the concentration dropped to 1.5 mg./ml. On paper electrophoresis at room temperature and pH 8.6, the cryoglobulin remained virtually at the start line. Fig. 2 shows the patterns using whole serum and cryoglobulin free serum.

The flocculation tests of liver function changed, the zinc sulphate and ammonium sulphate turbidities being markedly more positive in 1959 as might be expected from increasing globulin content of the serum. These tests were unaffected by temperature and whether done at 37° C. or room temperature, the results were much the same. The thymol turbidity and flocculation and serum colloidal gold tests however, although showing similar values in both years, were distinctly affected by temperature, being virtually normal when done at 37° C. but positive at room temperature. This would seem to imply that the cryoglobulin was largely responsible for their degree of positivity. The actual values obtained at various times can be seen in Table I. Serum cholesterol 337 mg./100 ml., serum calcium 9.2 mg./100 ml., blood urea 57–70 mg./100 ml., serum bilirubin 0.3 mg./100 ml. C.S.F. protein 50 mg./100 ml., no cryoglobulin detected.

Urinary protein was variable, the highest value obtained in 1957 was 320 mg./100 ml., this being all present as heat coagulable protein. In 1957, however, amounts up to 1400 mg./100 ml. were frequently found. No Bence-Jones protein or nucleoprotein were ever detected and on only one occasion was a trace of proteose found. Cryoglobulin was never detected in the urine. Percentage normal renal function decreased from 49.5% in 1957 to 28% in 1959, the respective blood ureas being 57 mg./100 ml. and 70 mg./100 ml. Urinary concentration and dilution was adequate and except for the finding of a very few granular casts in a single isolated specimen, nothing abnormal was ever seen in the deposit.

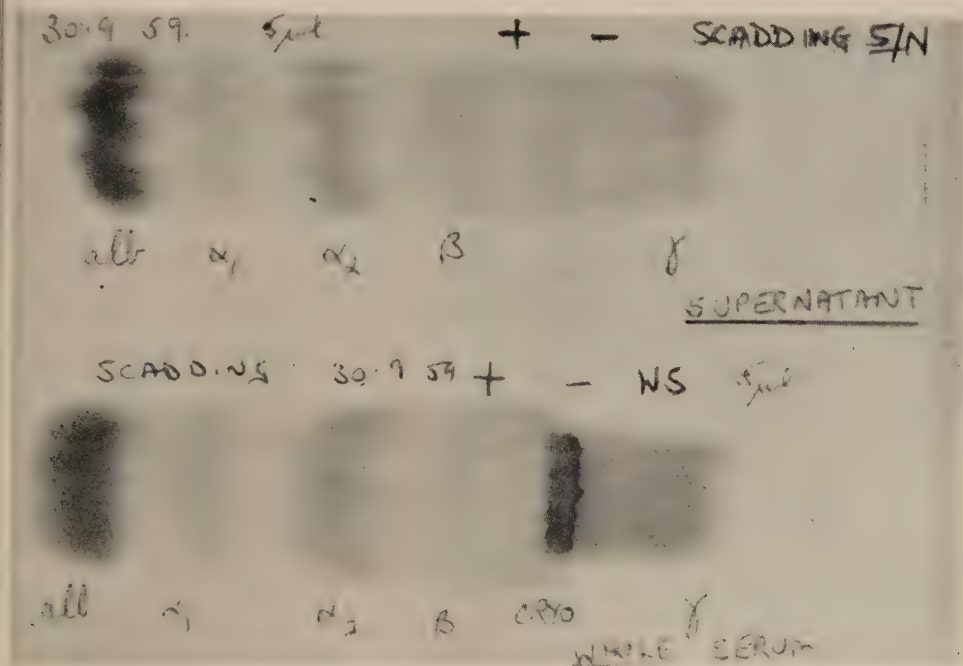


FIG. 2.

Skiagrams of skeleton showed no evidence of myelomatosis. Barium meal normal. B.M.R. 103% normal. E.C.G. showed some left ventricular hypertrophy.

Histology.—Recent skin lesion.—(i) First admission (1957). An area of skin showing central necrosis of the epidermis and dermis. The small blood vessels in the upper part of the dermis underlying the central zone have necrotic walls and were thrombosed as well as containing coagulated eosinophilic material. The adjacent connective tissues were infiltrated by acute inflammatory cells amongst which there were some eosinophils. There were similar vascular changes in the hypodermis and subcutaneous tissues. The larger vessels showed changes of endarteritis. A few smaller vessels showed actual arteritis.

(ii) Gangrenous finger.—The changes were similar to those described above. The digital artery showed subintimal proliferation and sclerosis with narrowing of the lumen and thrombosis.

(iii) Renal biopsy.—Third admission (1959). The glomeruli showed changes varying from diffuse thickening of the basement membrane of the capillary tufts to complete hyalinization. Some had collagen formation on the inside of Bowman's capsule. The

TABLE I.—*Results of Serum or Plasma Protein Analyses.*

Date	Whole serum or plasma			Cryoglobulin content in mg./100 ml.	Temp.	Cryoglobulin free serum or plasma					Whole serum or plasma				
	Albu- min	Glo- bulin	Total			T.T.	T.F.	S.C.G.	ZN	NH ₄	T.T.	T.F.	S.C.G.	ZN	NH ₄
4.4.57	3.95	2.35			R.T.						7	2	5	7	5
			6.30		37° C.										
20.5.57	3.59	2.34			R.T.	2	0	0	1	1	3	1	4	2	4
			5.93	1.81					440						
1.6.57	3.99	2.25			R.T.	1	0	0	1	1	2	0	4	5	5
			6.24	1.87					380						
16.9.59	3.10	3.63			R.T.	2	0	0	5	6	4	1	4	8	9
			6.73	3.13					500						
30.9.59	2.84	3.90			R.T.	2	0	0	7	8	5	2	5	14	12
			6.74	3.40	37° C.				500						
				6.24							3	0	0	14	14

T.T. = thymol turbidity. T.F. = thymol flocculation. S.C.G. = serum colloidal gold. ZN. = zinc sulphate turbidity. NH₄ = ammonium sulphate turbidity. R.T. = room temperature.

arteries showed considerable intimal thickening and the arterioles hyalinization of their walls.

Sections of the kidney *post mortem* showed very similar changes to those of the renal biopsy. These changes were patchy in distribution. The vessels showed very severe changes of extreme mucinous intimal arterial thickening and in some an arteritis confined to the intima. Although the glomerular histology was suggestive of a membranous type of glomerulonephritis, the changes were not nearly diffuse enough to warrant this diagnosis.

DISCUSSION.

None of the disease states commonly associated with cryoglobulins was found in this case : this together with a history extending over nine years has led us to regard this case as probably falling into the category of essential cryoglobulinaemia, although the histological changes might suggest the possibility of some as yet unidentifiable collagenosis.

The intravascular precipitation of cryoglobulin can produce a whole spectrum of clinical features. Thrombotic occlusion of larger vessels may produce Raynaud's phenomenon or frank gangrene as seen in this case and also in those reported by Cagudda (1952), Hutchinson and Howel (1953), Butler and Palmer (1955) and Barnett *et al.* (1956). Cutaneous ulceration was a prominent feature in our patient and has also been reported by Flemberg (1948), Rorvik (1950), Gunz (1956), and Volpe *et al.* (1956). Other changes described are purpura, cold induced urticaria, mottled pigmentation and bleeding from the nose and gums. Rarer symptoms include thrombosis of the retinal veins (Wintrobe and Buell, 1933) and deafness (Barr *et al.*, 1950).

In view of the *in vitro* characteristics of the cryoglobulin, it is tempting to deduce a similar cold stimulus for the clinical features. Together with most other observers, however, we were unable to produce focal lesions by the application of an ice-pack : Pelzig (1954) was able to induce purpura by the application of ice water for one hour. Localized changes on cooling have been observed by Barr *et al.* (1950) who used a biomicroscope to study the conjunctival vessels of a patient with cryoglobulinaemia. They observed aggregation of red cells and slowing of the circulation following the application of a tube of ice water to the eyelids : in some places there was segmentation and sludging of the column of blood with reversal of flow. There was persistence of these changes for several minutes after the withdrawal of the stimulus. Similar findings in the conjunctival vessels were reported by Steinhardt and Fisher (1955). Hansen and Faber (1947) investigated Raynaud's phenomenon in a case of aleukaemic leukaemia with cryoglobulinaemia, using finger plethysmography. They showed that there was no vasoconstriction, but that the pulse wave was transmitted into partially dilated vessels presumably containing the precipitated cryoglobulins. It may be that a more generalized level of blood cooling is required to initiate more severe changes. Our patient's mouth temperature was always within normal limits, and we were unable to demonstrate any defect

in her metabolic rate (B.M.R. 103%). It may be worth noting, however, that she developed a subjective intolerance to cold during her illness, and had resorted to wearing many layers of clothing before its therapeutic desirability was pointed out to her.

Acrocyanosis with Raynaud's phenomenon in association with the presence of cold agglutinins may produce a clinical picture akin to cryoglobulinaemia. Luckey *et al.* (1951) have compared and contrasted the precipitation characteristics of the two sera.

Barnet *et al.* (1956) in reviewing the literature found the average age incidence to be in the sixth decade. It is not surprising therefore that some of these cases of cryoglobulinaemia have evidence of hypertension and renal decompensation. The incident of cerebral thrombosis in our case was thought more likely to be due to the associated hypertension than to the presence of cryoglobulin.

Autopsy in a case of Lerner and Watson (1947) showed the changes of chronic glomerulonephritis. A specific renal lesion has not been described in cryoglobulinaemia, and histology in our case was not diagnostic. The abnormal globulins have not been described in the urine, presumably because of their large molecular weight.

A feature of this case was the gradually increasing normochromic anaemia. Barnett *et al.* (1950), in reviewing 27 cases, noted anaemia to be present in all but two. We could find no adequate cause for the anaemia and attribute it provisionally to gradually increasing renal failure.

Clinical manifestation in cryoglobulinaemia depends upon the severity of the thrombotic phenomena and the severity of the associated disease. Gunz (1956) described a case surviving thirteen years, Volpe *et al.*, one surviving twenty-five, while symptoms were present in our case for nine.

No specific therapy has been found of any value in cryoglobulinaemia. The management of the thrombotic episodes is symptomatic and prophylactic measures should be adopted to avoid chilling.

SUMMARY.

A case with a nine year history of recurrent skin ulceration due to cryoglobulinaemia is described. No associated disease could be found. The biochemical characteristics of the condition are described.

We wish to thank Dr. Joeke and Dr. R. H. Heptinstall (St. Mary's Hospital) for the renal biopsy and report, and Dr. R. A. Goodbody (Royal South Hants Hospital) for the autopsy report and sections of the kidney.

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ROYAL SOCIETY OF MEDICINE.

SECTION OF DERMATOLOGY.

President—Dr. HUGH GORDON.

21 April 1960.

Acrokeratosis Verruciformis (Hopf.)—Dr. P. D. SAMMAN.

A man aged 32.

History.—Since birth this man has had groups of flat wart-like lesions on various parts of his body but especially on the backs of his hands and the inner sides of his knees and lower thighs. They cause no trouble and do not increase in number. He says his father had similar lesions.

On examination.—Large numbers of flat-topped lesions in groups which clinically closely resemble plane warts.

Investigations.—Histologically there was some increase in the keratin layer but it did not have the basket-weave appearance of a plane wart. There was slight papillomatosis and some vacuolization of the prickle cells. The granular layer was increased in thickness. There was a mild round-celled infiltration of the superficial corium.

Tuberculous Ulcers.—Dr. I. SARKANY (for Dr. D. I. WILLIAMS).

A housewife aged 57.

History.—She came here two years ago from Cyprus and has been troubled by ulcers on the left leg for the past fifteen months. She was first seen at another hospital at the beginning of 1959 when one of the lesions was biopsied and is said to have shown the histology of a granuloma. No acid fast organisms were demonstrated at that time. She was then treated with antibiotics, developed a deep vein thrombosis of the left calf and was given anticoagulant therapy.

On examination.—There are numerous small, indolent, round shallow ulcers covered with thin crusts on the left foot and leg (Fig. 1). Some show a linear distribution. There are also some ill-defined intracutaneous nodules which appear to be the precursors of the ulcers. Systemic examination is negative. The blood pressure is 140/80.

Investigations.—Full blood count normal. E.S.R. 30 mm./hr. Blood W.R. negative. Skiagram of chest normal. Skiagram of left leg—"The bones of the foot are poorly calcified. There is some irregularity of the head of the fifth metatarsal." Mantoux 1/10,000 positive. Urine—acid reaction, a trace of protein, leucocytes ++, culture sterile. Blood urea 39 mg.%. Total serum proteins 7 g./100 ml. The electrophoretic pattern shown an increase in the α_2 globulin. Swabs from the ulcers—"Two of the three smears contained fragments of acid fast material which probably represented *M. tuberculosis*". Culture from a biopsy specimen taken on 19.ii.1960 has grown *M. tuberculosis*. Examination for leishmaniasis and pathogenic fungi was negative. A section shows a piece of skin in which there is a small central ulcerated area. From the ulcer there is a track containing fibrin and cellular debris which leads to a dermal cyst partially lined with stratified squamous epithelium. Within the lumen of the cyst there are numerous acute inflammatory cells and considerable cellular debris. Around the edge of the cyst there is a mixed acute and chronic inflammatory exudate together with several ill-defined non-caseating tubercle follicles. No organisms can be demonstrated in sections stained by Ziehl-

Neelsen's method, by the phloxinetartrazine method or by Geimsa's stain. Cystoscopy: No abnormality noted. An intravenous pyelogram was reported to show rather incomplete filling of the calyces of the lower pole of the left pelvis. Both kidneys are rather small and of the contracted type.

Treatment.—Occlusive bandages, local applications and systemic tetracycline have produced no improvement. Streptomycin 0.5 g. b.d. and INAH 100 mg. t.i.d. were started yesterday.

Comment.—The acid reaction of the urine, albuminuria and sterile pyuria as well as the appearances of the intravenous pyelogram suggest that she may have renal tuberculosis in addition to the ulcers. This type of tuberculous ulceration would appear not to belong to the group of tuberculous gummata.

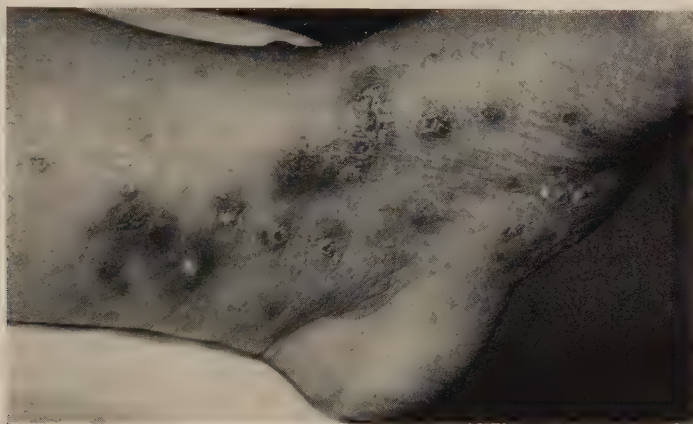


FIG. 1.

Dr. C. D. CALNAN: Is it a sporotrichotic type of tuberculosis of the skin? It appears to be going up the lymphatics.

Dr. J. S. PEGUM: I showed a Polish patient under the name mentioned at this Section. He had tuberculosis verrucosa cutis on one hand; and running up the arm, in echelon, was a series of abscesses from the pus of which plenty of tubercle bacilli were easily grown. In addition, he had a little patch of lupus on one part of the body and little subcutaneous lumps which felt as though they were lymph glands in quite unexpected places. I do not know whether that is so with this patient.

Dr. I. SARKANY: We found no subcutaneous lumps in this patient. There were, however, a few ill-defined intracutaneous nodules on the legs, which seemed to be the precursors of the ulcers.

The following cases have been published in *Proc. R. Soc. Med.*, 53, 963.

Two Cases of Vogt-Koyanagi-Harada Disease.—Mr. T. A. CASEY and Dr. P. D. SAMMAN.

Porphyria Cutanea Tarda.—Dr. D. SHARVILL.

The following cases were also shown.

Dermatofibrosarcoma Protuberans.—Dr. P. D. SAMMAN.

Pustular Psoriasis.—Dr. D. S. WILKINSON.

Alopecia Mucinoso (Pinkus).—Dr. A. W. MCKENZIE (for Dr. J. E. MOYNAHAN).

Occipital Nodules for Diagnosis.—Dr. D. G. G. BETT.

Multiple Metastatic Carcinoma of Skin.—Dr. B. SCHWARTZ.

Lichen Planus.—Dr. C. M. RIDLEY.

19 May 1960.

Lichen Planopilaris.—Dr. G. C. WELLS.

A man aged 36.

History.—Small bald patches were first noticed four years ago. When seen at St. John's Hospital in 1957 there were eight round patches of alopecia a centimetre and a half in diameter showing redness and follicular plugging. At that time there was widespread itching with follicular lichen planus scattered on the trunk and limbs and white streaking of the buccal mucosa. There was a previous history of seborrhoeic eczema. Biopsy from the scalp (1957) shows lichen planopilaris. In 1957, intravenous A.C.T.H. rapidly resolved his lichen planus. Six months later there was a relapse in the scalp with further loss of hair. Since then, courses of prednisone, methyl prednisolone and triamcinolone have been given, each for about three months, with intervals of several months between courses. The loss of hair seems to be checked while he is on steroids, but continues when treatment is stopped.

On examination.—Extensive scarring alopecia of the scalp. The rest of body is clear.

THE PRESIDENT: This patient came to see me privately just after he had been discharged from St. John's and of course I communicated with Dr. Wells. He had at that date slight scarring in the scalp and alopecia but not so extensive as he has today. I felt at the time that further continuation with steroids was not anticipated and suggested the more or less old-fashioned method of bismuth injections. These, however, were not given.

Dr. G. A. BECK: I am not quite clear about his response to steroids but understand that he improved with the first course. I should like to know whether the scalp cleared and there was any sign of regrowth of hair or whether the condition merely stopped spreading at the time. I gather that after the other three courses of steroids there was no effect at all, but that there was some improvement while he was taking them.

Dr. G. C. WELLS: While he is taking steroids the hair fall seems gradually to cease and the scalp becomes less red and scaly. On withdrawal of steroids there is very gradual progression of patchy baldness. Obviously there is no recovery in the sense of regrowth of hair.

Dr. LOUIS FORMAN: Lichen planus of the scalp does lead to alopecia and a varying degree of atrophy. Lichen planus responds to moderate dosage of steroids and a period of treatment of two months is usually adequate. It may relapse, and should relapse affect the scalp severely—enough, then a further period of treatment might be considered. The severity of the relapse could be judged by the depth of colour, by the papule formation, the follicular keratinization and alopecia. When atrophy of the skin and alopecia is established, very little, if any, benefit can be expected from steroids.

Ulcer of Right Eyebrow Region.—Dr. E. N. M. JOHNSTON (for Dr. G. C. WELLS).

A woman aged 64.

History.—This ulcerated granuloma has been present since 1950. In 1944, ulcers on the legs were treated by injection of lumbar ganglia (the diagnosis then being thromboangiitis obliterans).

From 1946 to 1950, red patches kept recurring on the anterior aspects of the thighs and arms and finally the left eyebrow. Each time, the patches became vesicular and bullous, leaving raw areas which slowly healed. These lesions were diagnosed by two dermatologists as artefacts. The patient was seen by two psychiatrists who disagreed, one supporting and one opposing the artefact diagnosis. Subsequently psychiatric treatment has been refused by the patient.

In 1950, after a red rough patch on the left eyebrow had been treated with superficial radiotherapy, the lesion spread rapidly across the forehead to involve the right eyebrow and lids, which became swollen and vision was completely obscured, and remained so, until in 1956 considerable healing took place during a three month in-patient observation period. Diplopia was then noticed and has persisted.

Between 1950 and 1956 during periods of in-patient treatment partial healing took place; treatments included antibiotics, A.C.T.H. and radiotherapy.

After each discharge from hospital the lesion relapsed. On many occasions black scabbing has been seen on parts of the ulcer and the surrounding skin has shown varying degrees of excoriation and oedema. Occasionally the left brow has been erythematous and swollen.

Since 1956 the lesion has shown no marked change. Her general health has been good apart from occasional attacks of sinusitis and on general examination nothing contributory was detected.

Investigations.—Hb. W.B.C. and E.S.R. normal. *Staphylococcus aureus* and *B. proteus* were cultured from the ulcer. Biopsies were performed in 1951, 1953, 1954 and 1956. Histologically, the main features have been chronic inflammatory changes and the presence of considerable numbers of mast cells.

It is regretted that the notes from 1951 to 1955 are missing. This case was shown at the R.S.M. in 1951 but apparently was not published.

Dr. G. C. WELLS : There is a quite remarkable massive mast cell infiltration.

Dr. J. S. PEGUM : Have other bones besides the skull been X-rayed ? I thought about the possibility of mast cell reticulosis. I have a patient at the moment who has dense sclerosis of the bones which shows particularly well in the femoral bones.

Dr. C. D. CALNAN : I support the possibility of mast cell tumour. Did not the tumour described by Degos (1951) present with a solid lump like this ? Dr. Feiwel's case (1955) was similar.

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Dr. H. T. CALVERT : Is this not a mast-cell tumour like that of the cat which may occur over the eye ? It is exactly like the pictures that have been shown.

Dr. S. C. GOLD : Are mast-cell tumours sensitive to irradiation ?

THE PRESIDENT : I take it it is generally felt that this is not an artefact ?

The following cases have been published in *Proc. R. Soc. Med.*, **53**, 965.

Histiocytosis X.—Dr. H. BUCK (for Dr. G. C. WELLS).

Acanthosis Nigricans, Juvenile Type.—Dr. J. G. HOLMES.

The following cases were also shown :

Two Cases of Angiokeratoma Corporis Diffusum.—Dr. E. H. JELLINEK (for Dr. H. J. WALLACE).

Angiokeratoma Corporis Diffusum.—Dr. DAVID WISE (for Dr. H. J. WALLACE).

Multiple Congenital Defects.—Dr. H. BUCK (for Dr. H. J. WALLACE).

Lymphocytic Infiltration of the Skin.—Dr. G. C. WELLS.

Sarcoidosis with Annular Skin Lesions and Alopecia of the Scalp.—Dr. E. WILSON JONES.

Pigmentary Skin Changes ? Systemic Scleroderma.—Dr. E. WILSON JONES.

Acrodermatitis Continua (Hallopeau).—Dr. C. D. CALNAN.

CORRESPONDENCE.

The Editor, 'The British Journal of Dermatology'.

SIR,

SAMUEL PLUMBE (1795-1837).

If re-opening the subject is not too tedious, I would like to make some amendments to my short paper on Samuel Plumbe which you published in June 1957. When I wrote it I had to rely on searches of parish records made by those in whose custody they were; I did not obtain access to them. The parish records of St. George's Church, Bloomsbury Way, W.C.1, have, since then, been deposited in the London County Council's Record Office in the County Hall, S.E.1, and I have studied them there. In the baptismal register I have now found the following entries concerning children of Samuel and Emma Plumbe:—

Samuel Alderson born 29th October 1824 in Great Russell Street, Margaret born at the same address on 29th December 1826 (the children were baptized together on 21st February 1827, and one wonders why there was the delay of over two years before the boy was christened); Kate, born at Bedford Place on 31st July 1831 and christened some three weeks later on August 23rd. I am a little uncertain about Kate, but think she is the child referred to in the family papers as Emma.

The fact that Samuel Plumbe, a St. Thomas's man, dedicated the first edition of his *Practical Treatise on Diseases of the Skin* (1824) to a Guy's surgeon, Sir Astley Cooper, thanking him for "instructions long since received as a pupil", was a little baffling. One knew, of course, that St. Thomas's Hospital was close to Guy's in the old days (according to Bassett and Brock, 1960, "on the opposite side of the street until it was forced to move by the coming of the railways in 1860") but had not realized how closely the life of the students of these two hospitals mingled. Cooper's life was written by his nephew Bransby Blake Cooper, F.R.S., and published in two volumes by John W. Parker, West Strand, London, in 1843: Bransby describes how his uncle would conduct his usual ward round at Guy's "until the clock struck two, when, almost as if by magic, the pupils would suddenly leave the ward, run across the street to St. Thomas's Hospital, and take their seats in the Anatomical Theatre. In a few minutes Mr. Astley Cooper would appear among them, lecture for an hour, and on leaving the theatre go to the dissecting room (still in St. Thomas's) and "cast an eye at every table". "At half-past three he usually left the Hospital, taking in his carriage one of his articulated pupils or dressers, either for the purpose of having his assistance at some private operation, or perhaps . . . to write for him while he dictated, in the course of his professional circuit,"—which might last until 6.30 or 7 p.m. The use of the word "pupil" in Samuel Plumbe's dedication and in the account of Astley Cooper's life seems to give a reasonable clue concerning the relationship between the Guy's surgeon and the Thomas's man.

Finally I owe the present Mr. Plumbe of Woking an apology for having made an error in regard to his initials. For J. V. H. please read J. P. H. Plumbe.

I hope these small addenda will be of interest.

Yours sincerely,

R. M. B. MACKENNA.

London, W.1.

REFERENCE.

BASSETT, W. and BROCK, R. (1960). *Lancet*, i, 774.

BOOK REVIEWS

DISEASES OF THE SKIN.*

THIS book is considerably bigger and better than *The Skin Diseases* which Marshall published in 1948 when he was working in Johannesburg: he is now Head of the Department of Dermatology at the Medical School of the University of Stellenbosch and his work is much more mature. He has endeavoured to provide a text which undergraduates and general practitioners may use and one which will serve as introductory reading for postgraduates: despite certain details to which exception can be taken he has largely succeeded in his purpose. For those who study in Europe the merit of the book lies in its comprehensiveness, for not only does he consider all the diseases we commonly encounter but he also includes a wide survey of tropical and sub-tropical maladies which we seldom see, and gives adequate descriptions of the cutaneous manifestations of the venereal diseases—including exotics such as *dichuchwa* and *witkop*; further, the book is exceptionally well illustrated, the author having taken much care to collect a great variety of sharply focused photographs from many sources and to enlarge or reduce these in accordance with the reader's needs: the publisher and printer are to be congratulated on the way the illustrations are reproduced. Many of the eruptions thus presented are in negro patients and it will probably be salutary for postgraduate students here to realize that eruptions which they sometimes see in somewhat modified forms (e.g. those of tuberculosis or syphilis) can be extremely severe and debilitating.

The writing of an opening chapter on the anatomy and physiology of the skin ought to be fairly easy: nowadays, because of the plethora of information available, it is one of the most difficult chapters to construct. One cannot say more about Marshall's opening chapter on these subjects except that it is reasonably adequate: He then presents a nicely illustrated chapter on histo-pathology, and chapters on diagnosis, principles of treatment and allergy before he sets off with eczema and dermatitis on his long consideration of dermatological disease.

Because we all have gaps in our knowledge and because all unwittingly most of us nurture a few quite erroneous beliefs, a book of such wide scope containing nearly 1000 pages written by a single author is bound to be bad in parts, and this one is no exception. Your reviewer cordially disliked some sections and hopes that at any rate those on ano-genital pruritus (which he finds execrable), atopic eczema, patch-testing and allergides will be re-written before another edition appears. Also he much disliked "the lucites" as the heading of a chapter concerning diseases caused by actinic rays, but any dismay caused by this neologism was negligible compared with the horror which struck him when he encountered "radiolucites" for dermatoses caused by radium and X-rays. Marshall does not say so, but one presumes that "lucites" is derived (via French literature) from *lux*, *lucis*-light, and if this is accepted then radiolucites is a misnomer.

It will be seen from these remarks that a hostile critic will not have much difficulty in finding sections of the book on which he can comment adversely: but, regarded as a whole, the work is of considerable interest, excellently produced, the illustrations (as has been implied) constituting a feature of special interest and importance, and the whole representing a very great effort made by a single author.

R. M. B. M.

* *Diseases of the Skin*. JAMES MARSHALL (1960). Edinburgh and London: E. and S. Livingstone Ltd. Pp. 944, 496 black and white illustrations. Price £4 4s.

DERMATOLOGY FOR THE GENERAL PRACTITIONER.*

THE authors have set themselves the task in this book of presenting the subject of dermatology, more or less in its entirety within the space of 308 pages, which include copious illustrations, index, etc., and it is to their credit that they have in great measure succeeded. The book is primarily intended for office practice or, what we would call in this country, the General Practitioner, and it is set out in a series of sections covering separately such subjects as the common dermatoses, regional diagnoses, diagnostic procedures, therapeutic adjuncts, multiple organ diseases, dermatological allergy (a gem of lucid thinking and precise writing) and dermatological counselling, based on physiology.

The text is clearly written, well printed, and the whole volume is a credit to its producers. The illustrations are profuse, and for the most part adequately depict the subject, always provided that the reader is familiar with the classical picture *in vivo*. Attached to the various sections is a short reference to the literature, which is perhaps over-restricted and a shade parochial.

The main fault in this book is inherent in its quality of condensation, to comply with which it has been necessary frequently to sacrifice the rather complicated truth for the more concentrated half truth. Any practitioner, however, who has assimilated all there is in this book and has had the time to read the articles suggested, is unlikely to trouble a dermatological consultant to any marked extent. It is, however, true to say that a considerable knowledge of dermatology is required in order to appreciate the value of this volume.

D. E. O.

AN ILLUMINATED NUT SHELL.*

MOST dermatologists at some time or another have the urge to write a text book for the utterly uninitiated, for the students of to-day and those of yesterday who neglected their chances, or only too often were never given any to neglect. Dr. Sauer teaches students in Kansas and, judging by this book, he teaches them jolly well; I am delighted he responded to his urge.

It is quite remarkable how much information he has packed into 230 pages in an orderly, concise and extremely readable manner in the first part of the book where he deals systematically with the commoner eruptions, infestations and tumours. The last 30 pages form a "Dictionary Index" in which practically every entity gets a well-chosen word or two. The whole book is profusely illustrated with really excellent black and white photographs (there must be over 300 of them) and there are also a large number of colour plates, some good and a lot bad, but it would be unfair to worry about these as they were given free by numerous drug houses with the result that the price has been kept down to a very reasonable level.

The difficulty in producing a book of this type is to make the various conditions real and not just lists of symptoms and signs, and at the same time know what to leave out. Inevitably there was little space for the natural history of diseases and this was particularly noticeable in the account of the bullous eruptions, but elsewhere potted case histories keep the text delightfully alive. Histopathology is entirely omitted, but there is a good section on the histology of normal skin. Treatment is kept simple and rational and is divided routinely into that of the acute and chronic stages with additions where necessary for any likely complications. Unfortunately

* *Basic Office Dermatology*. S. MADDIN, J. L. DANTO and W. D. STEWART. (1960.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. Pp. 308. Price £4 14s.

* *Manual of Skin Diseases*. GORDON C. SAUER (1960). Kansas: Pitman Medical. Pp. 269. 179 Illustrations. Price 70s.

many proprietary names are used which are unfamiliar to English readers. Anti-histamines are used perhaps to excess for relief of eczematous itching at the expense of straightforward sedation and at the end of every tiresome disease a paragraph tells the reader that steroids (triamcinolone seems the favourite) may be needed for a week or two. I do hope in the next edition for a short chapter on the "do's and don'ts" for systemic steroids. Keratoacanthomata seem to be different in Kansas if we are to believe the photograph on page 217 showing multiple encrustations of 4 years' duration on a leg. The only section, however, that I would really challenge seriously is that on haemangiomas, where the author most carefully points out in a cautionary tale the folly of leaving a superficial strawberry naevi alone and then goes on to advise radiotherapy for the deeper part of the mixed type extending subcutaneously. For the sake of the future practitioner, for whom this excellent book is intended, I must add my own epilogue, so that it can't be said of him that

He tells the sad story of Sarah Sue
Whose strawberry naevus grew and grew.
Its natural history he didn't know
So gave it a touch with CO₂ Snow

Envoi

Together they cry: "This scar of ours!
If only we'd listened to Simpson and Bowers".

I do seriously suggest to those who teach dermatology that they take a look at this book. They may well decide to recommend it to their students.

R. D. S.

BRITISH ASSOCIATION OF DERMATOLOGY.

THE method of selecting papers to be read at Annual Meetings was discussed by the Executive Committee of the Association on 17 November 1960. It was decided that as an experiment those who wish to read papers in July 1961 should submit them to the Hon. Secretary by the end of April in a form suitable for publication. This procedure should enable the selection committee to maintain a high standard of papers read at the meetings and should also facilitate prompt publication. A paper accepted to be read remains the property of the Association (see Rule 16) but this does not mean that it is automatically deemed suitable for publication in the Journal. The submission of manuscripts by April does not apply to those of speakers invited by the Association.

CURRENT LITERATURE.

“DELAYED” CUTANEOUS HYPERSENSITIVITY TO LEUKOCYTES IN DISSEMINATED LUPUS ERYTHEMATOSUS. E. A. FREEDMAN, W. A. BARDAWIL, J. P. MERRILL and C. HANAU. (1960) *New Engl. J. Med.*, **262**, 486.

Twenty patients with disseminated lupus erythematosus were given endodermal injections of autologous leucocytes. Sixteen showed a delayed cutaneous reaction at its maximum in twenty-four hours. Of the four who did not react, three were on steroids.

Two of seven patients with rheumatoid arthritis also produced a reaction, whereas only one of fifty with a variety of different diagnoses responded positively.

It is suggested that a cellular or humoral antibody to nucleoprotein may be responsible for the reaction.

A. D. P.

BASAL-CELL CANCER IN CHILDREN AND YOUNG ADULTS. J. E. MURRAY and B. CANNON. (1960) *New Engl. J. Med.*, **262**, 440.

The histories of forty-one patients with basal-celled carcinoma are reviewed. All were under thirty years of age. In twelve cancer was diagnosed between sixteen and twenty years and in sixteen between twenty-six and thirty.

In thirty-two there was a history of a previous lesion, usually a papilloma, naevus or scar, which was injured before cancer appeared.

A. D. P.

THE OCULAR COMPLICATIONS OF CHLOROQUINE THERAPY. H. E. HOBBS and C. D. CALNAN. (1958) *Lancet*, i, 1207.

Of 30 patients under treatment with chloroquine, mainly for lupus erythematosus and actinic dermatitis, 19 complained of one of the following: disturbances of vision, blurring of vision, haloes around lights, focusing difficulties and other visual sensations.

Under slit lamp examination some of the symptomless patients showed corneal changes while some of those complaining of symptoms showed none. Several types of corneal change were seen, all confined to the epithelium of the cornea with slight changes in the stroma immediately underlying Bowman's membrane in a few. The changes were white dots irregularly scattered over the corneal surface. In some patients the dots were aggregated into faint curved white lines just below the pupil while the most severely affected patients showed an irregular line of whitish deposit in the subpupillary region as well as the widespread white dots. This line was faintly yellow in a few cases. When chloroquine was stopped the corneal changes showed gradual recession and in some cases complete resolution, but the authors indicate that at least one case shows continued loss of visual acuity and point out the need for careful ocular supervision during treatment with antimalarials.

R. H. M.

GRAVITATIONAL LEG ULCERS IN THE ELDERLY. STANLEY RIVLIN. (1958) *Lancet*, i, 1363.

This is an account of the standard method of treatment at the London Varicose Clinic. The aim of treatment is to abolish oedema of the affected extremity. This is achieved by applying an adhesive bandage to the leg and advising the patient to wear suitable footwear and to take suitable and adequate exercise. The wearing of a thin elastic all-way stretch bandage is advised to prevent recurrence.

R. H. M.

NUCLEAR CHANGES IN ORAL EPITHELIAL CELLS IN SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD DUE TO VITAMIN-B₁₂ DEFICIENCY. S. T. BOEN, J. A. MOLHUYSEN and J. STEENBERGEN. (1958) *Lancet*, ii, 294.

Nuclear changes in oral epithelial cells of patients with pernicious anaemia have previously been described. The changes consist of marked nuclear polymorphism together with giant nuclei. This change is now described in the rare example of vitamin B₁₂ deficiency manifested by neurological disorders without haematological changes. The technique of demonstrating this change is described.

R. H. M.

PENICILLIN SENSITIVITY IN PATIENTS WITH BURNS. M. R. DAVIES. (1958) *Lancet*, ii, 345.

Of 1232 patients receiving topical penicillin cream for burns 0.5% showed a skin reaction which may have been due to allergy to penicillin. No eczematous type of reaction is described except possibly under the heading "Localized Type of Reaction".

Of patients receiving intramuscular penicillin 7.4% showed a reaction in the skin. No patch tests or intracutaneous tests were carried out.

R. H. M.

SKIN TRANSPLANTATION IMMUNITY IN RELATION TO HYPERSENSITIVITY. L. BRENT, JEAN BROWN and P. B. MEDAWAR. (1958) *Lancet*, ii, 561.

The reaction against skin homografts in guinea-pigs can be made to express itself as a hypersensitivity reaction of the delayed type. Two reactions are described (a) a "direct reaction" in which antigenic matter extracted from the tissues of a homograft donor is injected intradermally into a sensitized recipient; and (b) a "transfer reaction", in which cells taken from the regional lymph nodes of a sensitized recipient are injected intradermally into the homograft donor.

The transfer reaction is thought to represent a passive cellular transference of the state of sensitivity revealed by the direct reaction. The transfer reaction was not elicited by "immune" serum or by heat-killed lymphoid cells. The occurrence of these reactions strengthens the analogy between skin transplantation immunity and other immunological reactions that are thought to be mediated through cells. (Authors' summary.)

R. H. M.

NEPHROTIC SYNDROME AFTER THE APPLICATION OF MERCURY OINTMENT. N. E. WILLIAMS and H. G. T. BRIDGE. (1958) *Lancet*, ii, 602.

A patient with psoriasis who had applied an ointment containing 5% of ammoniated mercury to the affected areas intermittently for ten years developed the nephrotic syndrome. Urinary excretion of mercury was high (240 μ g. in 24 hours). After treatment with dimercaprol (BAL) the urinary excretion increased—during one period fivefold—and then decreased so that by the eighteenth day the daily excretion of mercury was 84 μ g. Five months later the patient was completely well and blood and urine findings were normal.

R. H. M.

ARMADILLO. A PROTECTIVE CLOTHING AS A SHIELD FROM X-RADIATION. J. M. TANNER, R. H. WHITEHOUSE and J. H. POWELL. (1958) *Lancet*, ii, 779.

The authors have designed and had manufactured a new material "Armadillo" consisting of a series of lead scales each sealed in a flexible plastic envelope and imbricated so as to overlap its next door neighbour above, below and from side to side. It is very flexible and can be manufactured into suitable garments to protect the gonads of patients and radiographer of both sexes, or indeed any desired part of the body.

R. H. M.

NEUROLOGICAL SYNDROMES ASSOCIATED WITH CARCINOMA. Sir RUSSELL BRAIN and RONALD A. HENSON. (1958) *Lancet*, ii, 971.

This is a review of the various neurological disorders occurring in carcinoma independently of the presence of metastases. The interest to dermatologists is the occurrence of dermatomyositis in association with carcinoma. One of the 42 patients described showed dermatomyositis and 8 showed no clinical evidence of neural lesions. The authors prefer to use the term "carcinomatous myopathy" in preference to polymyositis.

R. H. M.

IMMEDIATE EFFECTS OF IRRADIATION OF ELASTIC TISSUES WITH X-RAYS, RADIUM, AND RADIOACTIVE COBALT. STEFAN JELLINEK. (1958) *Lancet*, ii, 1149.

Postmortem radiation experiments were carried out on the ligamentum nuchae of foetal calves and on human skin to study the immediate effects on elastic tissue. Irradiation produced a wide range of morphological changes in the compact elastic tissue of the ligaments from slight curling to disruption and dislocation of the majority of the fibres. In human skin similar changes occurred as well as marked changes in the vessel walls of subcutaneous blood vessels. Changes were found in the whole range of dosage irradiation used down to 1 r. the lowest dose used.

R. H. M.

ACUTE PANCREATITIS COMPLICATING PREDNISOLONE THERAPY. MARTIN S. BOURNE and HUGH DAWSON. (1958) *Lancet*, ii, 1209.

The association between pancreatitis and administration of corticosteroids was first noted in rabbits given cortisone experimentally. Postmortem findings on patients dying from various

causes while on corticosteroid therapy have shown evidence of acute pancreatitis. The patient described here developed acute pancreatitis while being treated with prenisolone for type II nephritis. The diagnosis of pancreatitis rested on the occurrence of abdominal pain and a rise in serum amylase. The patient recovered satisfactorily.

R. H. M.

ORAL TREATMENT OF RINGWORM WITH GRISEOFULVIN. D. I. WILLIAMS, R. H. MARTEN and I. SARKANY. (1958) *Lancet*, ii, 1212.

This is the account of the first clinical trial of griseofulvin in human patients. Nine patients with *T. rubrum* infection of the skin or nails were treated and within two weeks the skin appeared clinically normal although fungus was found in skin scrapings in two patients as long as a month after stopping treatment. Infected nails started to grow out with increasing extent of normal nail below the infected areas. One child with *M. audouini* infection of the scalp and face showed clearance of the skin lesions in two weeks and normal hair growth proximal to the infected part after three weeks. No side effects were noted. The dose given was 0.5 g. four times a day.

R. H. M.

CLEANSING OF THE NORMAL AND ABNORMAL SKIN. E. KEINING. (1959) *Derm. Wschr.*, 140, 1245.

Synthetic detergents are being used increasingly in Germany instead of soap, and the author quotes American sources stating that the proportional sale of detergents in the United States is now 90% compared with 10% of soaps.

Soaps as well as detergents are degreasing agents which is no real disadvantage as according to the author 90% of the population are seborrheics.

A detergent cake of slightly acid pH was used in various pathological conditions and most gratifying results were achieved in chronic furunculosis, monilial paronychia, trichomycosis, erythrasma, pityriasis versicolor, dysidrosis, miliaria rubra and particularly acne vulgaris.

There is no calcium precipitation on the normal skin and there were no sensitization reactions. Oedema of the skin was reduced and the acid pH ensures that the acid mantle of the skin is maintained which reduces the flora of the skin.

J. M.

MUCIN. A COMPARATIVE STUDY OF HISTOPATHOLOGICAL STAINING REACTIONS. L. H. WINER and E. T. WRIGHT. (1959) *Derm. Wschr.*, 140, 1281.

Mucin is secreted by mucinous glands. Pseudomucin of a gelatinous breast carcinoma is similar to true mucin as far as staining properties and origin are concerned. Diffuse and pre-tibial myxoedematous degeneration of the connective tissue does not take up periodic Schiff stain and the same applies to mucinosis follicularis which is essentially a degeneration of the epithelial cells of the sebaceous glands and hair follicles. An inflammatory cell reaction was observed in the vicinity of the mucoid epithelial degeneration of mucinosis follicularis.

All types of mucin take up alcian blue and thioimin before or after treatment with 0.5% diastase. Periodic acid Schiff stain and periodic Schiff alcian blue stain differentiate mucin from myxoedematous degeneration (diffuse and pre-tibial) as well as mucinosis follicularis.

J. M.

ANOGENITAL VEGETATING AND CIRCUMSCRIBED PAGET'S DISEASE. H. TELLER. (1959) *Derm. Wschr.*, 140, 1305.

Two unusual cases of extramamillary Paget's disease are described.

One patient showed partially vegetative lesions on the scrotum and root of penis. Histologically a typical picture of Paget's disease but also particularly in the vegetating area, changes suggesting Bowen's disease were found.

The second case situated in the perianal area exhibited epidermal and cutaneous pigmentation particularly at the periphery.

J. M.

OBSERVATIONS ON A CASE OF ATROPHODERMIA VERMICULATA. T. SCHULZ, E. BOTEZAN and N. GANEA. (1959) *Derm. Wschr.*, 140, 1346.

A male patient aged 20 showed all "conditional" signs (pseudo-comedones, acneiform folliculitis, erythematous and pigmentary macules) simultaneously or over a period of time. The classification into four types (Darier with pseudo-comedones, Pautrier showing macules, Brocq Besnier with folliculitis and Zoon-Bruck-Photinos-Oppenheim with atrophic scars without preceding cutaneous changes) is questioned.

It is postulated that this polymorphism may well be present in all cases, if followed up for a sufficiently long period of time or otherwise a fifth, mixed type should be added in the classification.

J. M.

VACCINIA GENERALISATA HETERO-INOCULATA IN ADULTS. G. KOBER and W. ROHDE. (1959) *Derm. Wschr.*, **140**, 1361.

One male patient suffering from reticulosarcoma and a physician affected by atopic eczema developed generalized vaccinia after contact with recently vaccinated children. The former patient died whilst the latter recovered.

The author feels that patients suffering from eczema are almost certain to succumb when they contract smallpox and he rightly stresses the increased possibility of contagion through modern traffic.

He suggests that patients suffering from atopic eczema be vaccinated against smallpox in a specialized in-patient unit with prophylactic steroid therapy at the end of the viraemic phase (just before the maculo-papular stage).

J. M.

THE DIFFERENTIAL DIAGNOSIS OF MOLLUSCUM PSEUDO-CARCINOMATOSUM. TH. GRUNEBERG. (1959) *Derm. Wschr.*, **141**, 1.

Glycogen content established by the P.A.S. reaction is useful in the differential diagnosis of molluscum pseudo-carcinomatousum and squamous cell epithelioma. Keratoacanthoma always contains glycogen whilst only some squamous cell carcinomata give a positive reaction.

The clinical and histological diagnosis of keratoacanthoma is, in the author's opinion, doubtful in case of a negative P.A.S. reaction. It is, however, important not to examine only peripheral portions of the lesion. Thirty-eight cases of keratoacanthoma were examined, all of which gave a positive P.A.S. reaction whilst 8 cases out of 35 of squamous cell carcinoma did not contain glycogen.

J. M.

THE "TRAVELLING" IRRADIATION FIELD OF CHAUL THERAPY. P. MÖSLEIN. (1959), *Derm. Wschr.*, **141**, 10.

Large lesions are often difficult to treat by Choul's "close therapy". Using the largest applicator No. 8 (4.5 cm. diameter) the larger lesions were divided into 2-6 fields. Lead rubber circular dishes of a diameter of 4.49 cm. 2 mm. thickness with 0.8 mm. lead are used to cover the irradiated field and the adjoining area is irradiated the next day etc. until the whole affected region has been treated with adequate shielding. Single dose of 500 r per field, total dose 12×500 r is being used.

J. M.

KERATOACANTHOMA: A REVIEW OF HISTOPATHOLOGICAL SPECIMENS PREVIOUSLY DIAGNOSED AS KERATOACANTHOMA OR AS SQUAMOUS CELL CARCINOMA OF THE SKIN. WILLIAM S. BROTHERS, WILLIAM N. NEW and WALTER R. NICKEL. (1960) *Arch. Derm., Chicago*, **81**, 369.

Of 233 specimens taken from 1951 to 1957, 214 were originally diagnosed as squamous cell carcinoma and 19 as keratoacanthoma. When these sections were reviewed, 21 were considered to be keratoacanthoma and not squamous cell carcinoma making in all 40 or 17% keratoacanthoma. Before 1954 all these lesions would have been considered squamous cell carcinoma.

J. K.

2,5-DIHYDROXYPHENYLPYRUVIC ACID AND COLLAGEN DISEASES. MURRAY, J. TYE, SHERMAN MASTERS, BERNARD APPEL, HERBERT WHITE, TAKEHIKO TANAKA, W. E. KNOX ANDREA CULLEN and BARBARA ROSEN. (1960) *Arch. Derm., Chicago*, **81**, 447.

The authors investigated the claim that the inability of patients to metabolize phenylalanine and tyrosine completely led to the appearance in the urine of 2, 5-dihydroxyphenylpyruvic acid, but they failed to demonstrate its presence in the urine of 10 patients suffering from lupus erythematosus, rheumatoid arthritis or periarteritis nodosa.

J. K.

ZOSTER WITH INVOLVEMENT OF THE BLADDER MUCOSA. F. LEHMANN and K. FELKL. (1958) *Zbl. Haut. u. GeschlKr.*, **24**, 9.

Report of two cases of herpes zoster of the genital area with involvement of the bladder mucosa. Seen on cystoscopy.

P. D. C. K.

OEESOPHAGEAL STENOSIS IN PEMPHIGUS. R. SCHMITZ. (1958) *Zbl. Haut. u. GeschlKr.*, **24**, 36.

Severe oesophageal stenosis in a case of pemphigus vulgaris of 8 years' duration. The oesophageal obstruction was cleared by a short course of prednisone.

Probably the diagnosis was benign mucous membrane pemphigoid since only mucosae were affected. P. D. C. K.

FAVRE-RACOUCHOT DISEASE. H. KRUGER, H. DORN and H. WEISE. (1958) *Zbl. Haut. u. GeschlKr.*, **24**, 83.

A reminder of the correct label for a not uncommon but seldom recognized disorder, nodular cutaneous elastosis with cysts and comedones. Pictures and histology. P. D. C. K.

NAEVUS SYRINGOCYSTADENOMATOSUS PAPILLIFERUS ON A NAEVUS SEBACEOUS. W. UNDEUTSCH and H. FRIEDRICH. (1959) *Zbl. Haut. u. GeschlKr.*, **27**, 129.

The appearance was that of a pyogenic granuloma. Literature, clinical and histological report with pictures of this unusual combination. P. D. C. K.

KAPOSI'S HAEMORRHAGIC SARCOMA OF THE ORAL MUCOSA. H. DORN and F. SCHMAROW. (1959) *Zbl. Haut. u. GeschlKr.*, **27**, 138.

A woman aged 80 with skin lesions of Kaposi's sarcoma for 8 years. After 6 years typical lesions were seen on the hard palate, in the cheeks and under the tongue. Histology and pictures. P. D. C. K.

HERPES SIMPLEX AND VARICELLA-ZOSTER. F. O. MACCALLUM. (1959) *Practitioner*, **183**, 587.

The virus of herpes simplex may produce a variety of diseases, such as acute gingivo-stomatitis, rhinitis, keratoconjunctivitis and keratitis, meningo-encephalitis, infection of the genitalia and, occasionally, a disseminated systemic disease.

It seems evident that many mothers do not possess the herpes simplex antibody and it is possible for infants up to the age of three months to develop severe herpetic infection from midwives, nurses and attendants in maternity wards and nurseries.

The viruses of varicella and zoster are probably identical, being the same size and shape and having identical cytopathic effects in tissue culture. It seems likely that zoster has an accelerated antibody response when occurring in someone who has previously had varicella.

There is no specific treatment for either condition and it is possible that cortisone is contra-indicated in patients with varicella or zoster. R. J. C.

NODULAR PRURIGO OF HYDE. J. GAY PRIETO, A. P. RODRIGUEZ PEREZ, G. JAQUETI, S. NOGUER-DEBRAY and G. ARANA. (1959) *Actas dermo-sif., Madrid*, **50**, 3.

In describing two cases of nodular prurigo, besides the well-known banal histological findings of this condition, the authors record two unusual histological features. The first was an intense melanin pigmentation of the epidermis. The second feature was that abundant swollen cells resembling mastocytosis were found in the dermis, as well as the nerve tissue changes.

They found local hydrocortisone injections effective in relieving the pruritus as well as greatly reducing the height of the nodules. Normal saline injection had practically no effect. P. I.

SEVERE URTICARIA FOLLOWING ERYTHROMYCIN THERAPY. A. S. PRASAD. (1960) *New Engl. J. Med.*, **262**, 139.

A report on urticaria, believed to be an allergic reaction to erythromycin. A. D. P.

TRIAMCINOLONE IN DERMATOLOGIC CONDITIONS. E. F. FINNERTY. (1960) *New Engl. J. Med.*, **262**, 176.

The author states that "routine cases of acute contact dermatitis, generalized eczematoid dermatitis, sensitization dermatitis and generalized nummular eczema can be completely cleared without relapse" within ten days on triamcinolone.

The dosage recommended is 4 mg. four-hourly, reduced at forty-eight hour intervals until no more is being given in eight to twelve days. A. D. P.